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"HYPOKALEMIA IN ORGANOPHOSPHORUS COMPOUND POISONING"

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CERTIFICATE

This is to certify that the dissertation entitled **"HYPOKALEMIA IN ORGANOPHOSPHORUS COMPOUND POISONING"**is a bonafide work done by **DR.I.MARIRAJ**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2011 - 2014.

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DECLARATION

I solemnly declare that the dissertation entitled **"HYPOKALEMIA IN ORGANOPHOSPHORUS COMPOUND POISONING"**is done by me at Madras Medical College, Chennai-3 during July 2013 to December 2013 under the guidance and supervision of Prof. S.TITO, M.D., to be submitted to The TamilnaduDr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I.

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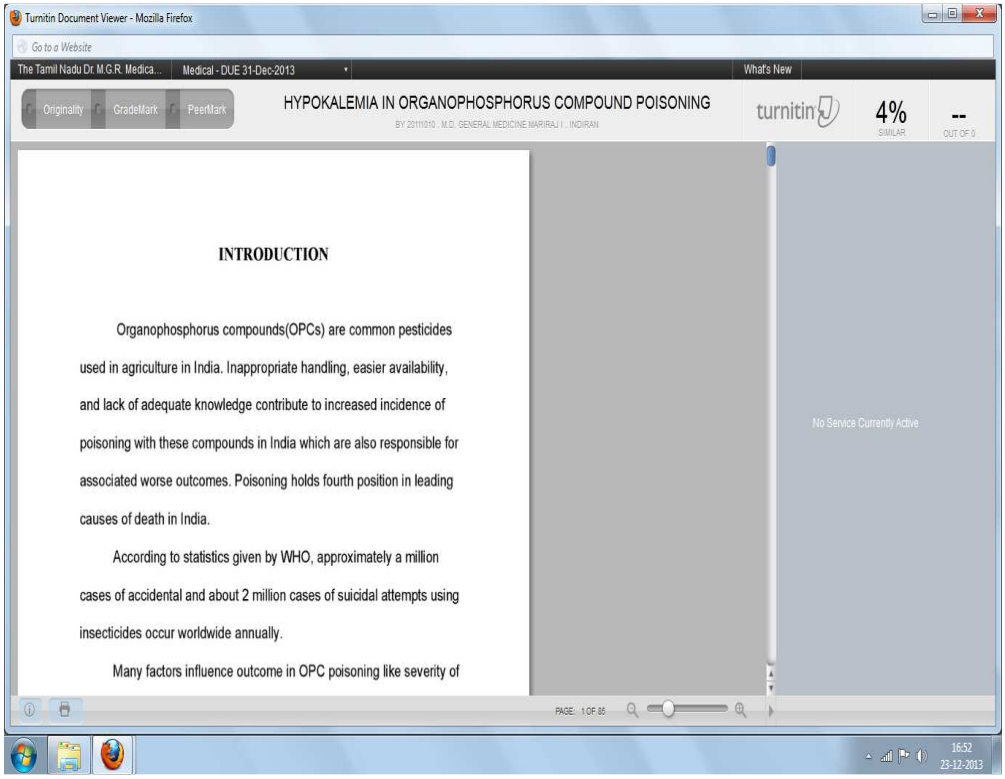
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INTRODUCTION
Organophosphorus compounds(OPCs) are common pesticides used in agriculture in India. Inappropriate handling, easier availability, and lack of adequate knowledge contribute to increased incidence of poisoning with these compounds in India which are also responsible for associated worse outcomes. Poisoning holds fourth position in leading causes of death in India.
According to statistics given by WHO, approximately a million cases of accidental and about 2 million cases of suicidal attempts using insecticides occur worldwide annually.
Many factors influence outcome in OPC poisoning like severity of
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ABBREVIATIONS

OPC	-	Organophosphorus compounds
WHO	-	World Health Organisation
TEPP	-	Tetraethylpyrophosphate
GIT	-	Gastro Intestinal Tract
ACh	-	Acetyl Choline
CNS	-	Central Nervous System
AChE	-	Anticholine Esterase
BuChE	-	Butyryl Choline Esterase
RBC	-	Red Blood Corpuscle
BP	-	Blood Pressure
CVS	-	Cardio Vascular System
ARDS	-	Acute Respiratory Distress Syndrome
OPIDN	-	Organic Phosphorus Induced Delayed Neuropathy
EDTA	-	Ethylene Diamine Tetra Acetate
EMG	-	Electromyogram
ECF	-	Extra Cellular Fluid
ICF	-	Intra Cellular Fluid
ENaC	-	Apical sodium channel
CKD	-	Chronic Kidney Disease
GFR	-	Glomerular Filtration Rate
ARB	-	Angiotensin Receptor Blockers
ACEI	-	Angiotensin Converting Enzyme Inhibitor
RTA	-	Renal Tubular Acidosis
HypoKPP	-	Hypokalemic Periodic Paralysis

CONTENTS

ABSTRACT

BACKGROUND:

Organophosphorus compound(OPC) poisoning is very common in india and it is a very important cause of morbidity and mortality in such patients. Many factors determine the outcome in OPC poisoning. But so far, there are no properly conducted case control studies to analyse individual parameters in OPC poisoning. Hypokalemia is common in this scenario, and case reports are available which quote its significance.

AIM:

In this study of 50 patients, the impact of hypokalemia in OPC poisoning, has been studied.

EXCLUSION CRITERIA:

Diseases or drugs that can modify serum potassium levels have been excluded from the study.

OBSERVATION AND RESULTS:

In this study hypokalemia was associated with increased mortality and prolonged duration of mechanical ventilation, both of which are statistically significant with p values of 0.039 and 0.037 respectively.

CONCLUSION:

Hypokalemia can be used as a reliable and cost effective marker of worse outcomes in the setting of OPC poisoning.

KEY WORDS:

OPC poisoning, Hypokalemia, mechanical ventilation, atropine, pralidoxime and respiratory failure.

INTRODUCTION

Organophosphorus compounds (OPCs) are common pesticides used in agriculture in India. Inappropriate handling, easier availability, and lack of adequate knowledge contribute to increased incidence of poisoning with these compounds in India which are also responsible for associated worse outcomes. Poisoning holds fourth position in leading causes of death in India.

According to statistics given by WHO, approximately a millioncases of accidental and about 2 million cases of suicidal attempts usinginsecticides occur worldwide annually.

Many factors influence outcome in OPC poisoning like severity of poisoning, development of respiratory failure, availability of mechanical ventilation and so on.

In the current study, i am trying to assess hypokalemia in OPC poisoning and its impact on the outcome.

AIMS AND OBJECTIVES

1) To assess hypokalemia in the setting of OPC poisoning

2) To correlate hypokalemia with various clinical parameters and outcome.

REVIEW OF LITERATURE

Organophosphorus(OPCs) insecticides are one of the most commonly used insecticides in India and Asia.(1) Annually it is responsible for almost 2,00,000 deaths.(2) In some instances, severe poisoning may occur as an occupational hazard. Organophosphorus insecticides possess anticholine esterase property. It is not a common health issue in developed nations because access to poisons are restricted. Tetraethylpyrophosphate (TEPP), was the first Organophosphorus insecticide to be developed. Organic phosphorus compounds (OPCs) and carbamates are routinely used in India. These insecticides possess anticholine esterase property.

WHO classification of insecticides include five group

Extremely hazardous - Class Ia,

Highly hazardous - Class Ib,

Moderately hazardous - Class II,

Slightly hazardous - Class III , and

"Active ingredients unlikely to present acute hazard in normal use".

In our toxicology ward, following classification system is being used.

HIGHLY TOXIC:

Monochrotophos,

Phosphomidan,

Ethyl parathion,

Chlorthophos,

Demeton S Methyl,

Carbophenothion,

Methyl parathion, and Phroate.

MODERATELY TOXIC:

Fenthion,

Formothion,

Malathion,

Fenitrothion,

Diazinon,

Temephos,

Chlorpyriphos, and Methyl primiphos.

OTHERS:

Ediphenophos,

Phosphenidon,

Triazophos,

Azinphos,

Dimethoate,

Parathion,

Prophenophos,

Quinalphos, and

Jodfenphos.

Poisoning can occur either accidentally or intentionally. Direct contact through skin can be lethal. Chemically OPCs are classified into four groups,

Phosphorylcholines – group 1,

Fluorophosphates – group 2,

Cyanophosphates – group 3 and

Multiple constituents – group 4.

PHARMACOLOGY:

A syndrome of cholinergic excess results from inhibition ofanticholineesterase enzyme leading to accumulation of ACh in concerned receptors. If anticholineesterase enzyme is inhibited before the poison is metabolised in the body they are known as directly acting OPCs(oxons). But majority of commonly used OPCs such as parathion and malathion are prodrugs only. These compounds bind at the active site of anticholine esterase enzyme in the hydroxyl group. This chemical reaction inactivates the enzyme efficiently. This also results in development of a reversible but stable bond between the enzyme and the OPC. Because of reversibility of the bond, the active state of enzyme can be regenerated which is accelerated by the oximes such as obidoxime and pralidoxime. However if the oximes are not

administered early and sufficiently the bond between the enzyme and poison become irreversible by a phenomenon known as “ aging”.

Once this happened the enzyme cannot be reactivated by the oximes. (3) After aging has occurred the De-novo synthesis of enzyme is required to replenish enzyme levels.

PHARMACOKINETICS:

OPCs are absorbed well following

inhalation,

ingestion or

skin contact and

through GIT,

lungs,

mucous membranes and conjunctiva.

Presence of prior skin disease enhance absorption and toxicity.(4) poisoning can be divided into acute or chronic even though such a classification may not be relevant clinically. OPCs are highly lipid soluble so their volume of distribution is large. So they are accumulated in tissues and fat and protected from detoxification by metabolism.

Concentrations are highest in adipose tisssues. Recurrence of cholinergic crisis may occur following their redistribution into circulation.

OPCs which are prodrugs, are activated by cytochrome P 450 enzymes. CYP3A4, CYP2B6 and CYP1A2 are few examples of them. It occurs mainly in liver and intestinal mucosa.(5)

PATHOPHYSIOLOGY:

ACh is the neurotransmitter in

autonomic ganglia both sympathetic and parasympathetic,

neuromuscular junction of skeletal muscles,

postganglionic parasympathetic nerve endings,

secretomotor fibres to sweat glands, and

synapses in CNS.

During neurotransmission ACh is released into the synaptic cleft and binds to the receptors in postsynaptic membrane. These receptors are divided into muscarinic (present mainly glands of various organs, heart,GIT and CNS) and nicotinic(present in the autonomic ganglia and neuromuscular junctions). Muscarinic receptors are G protein coupled receptors and nicotinic receptors are ligand gated ion channels.

Stimulation of these receptors result in generation and propagation of action potentials or other post synaptic events.Normallyanticholine esterase deactivate ACh into acetate and choline.

Following its release into synaptic cleft ACh is rapidly hydrolysed. Choline reuptake into the presynaptic terminal is mandatory for the regeneration of ACh. Apart from skeletal muscles and nervous tissue AChE is also found in RBCs the levels of which almost correlates with enzyme activity of nervous tissue in the acute setting.(6)

Butyryl choline esterase (BuChE) is found in

plasma,

CNS ,

heart,

pancreas and

hepatic tissue.

It is synthesised in the liver. Its activity can be assessed and has important clinical utility particularly in anaesthesia.

Majority of clinical features of OPC poisoning is due to AChE inhibition, many other enzymes are also susceptible. Its signifigance is not known. (7) Usually commercially available insecticides contain coformulants other than OPCs. The ingestion of these substances also occur in settings of

poisoning, their effects are difficult to assess clinically. These coformulants contain surfactants and organic solvents.

Following inhalation they can cause aspiration pneumonitis, the risk of which is substantially high following coma and respiratory distress that occurs in OPC poisoning. Its management is difficult.

CLINICAL FEATURES:

ACUTE SYMPTOMS:

Clinical features are due to excessive activation of cholinergic in the above mentioned sites.

Typical patient is with severe poisoning, one who is

comatose,

pinpoint pupils,

paralysis of muscles,

sweating,

loose stools,

excessive lacrimation,

oral secretion and

odour of OPC.

Findings will not be typical in less severe poisoning. The onset of clinical features depends upon severity, route and individual OPC.

Clinical features can be summarised as follows:

SYMPATHETIC MANIFESTATIONS:

CNS:

disorientation,

delirium,

hallucinations,

unconsciousness, and

seizures.

OTHERS:

pupillary dilatation,

tachycardia,

increased BP,

retention of urine and

hyperglycemia

PARA SYMPATHETIC MANIFESTATIONS:

CNS:

Confusion,

delirium,

coma and

convulsions

OTHERS:

Papillary constriction,

increased lacrimation,

excessive salivation,

bradycardia,

bronchospasm,

diarrhoea and,

bladder incontinence

SKELETAL MUSCLES:

Neuromuscular weakness,

fasciculations and

paralysis.

Patients consuming large amounts of poison and directly acting OPCs will manifest within few minutes after consumption. Almost all the patient will show symptoms within 24 hours. Lipid solubility of OPCs also determine the toxicity. Compounds with high fat solubility are distributed fast into the fat stores. So their toxicity will be somewhat less.

But the symptom of toxicity will worsen as redistribution of the poison occurs.

The occurrence of respiratory paralysis may be delayed with compounds with high lipid solubility like fenthion than compounds with low lipid solubility.(8) Other features of poisoning which includes persistent cholinergic signs can occur for a longer duration in compounds with high fat solubility as they are released into the circulation again.

Patients may have variety of CNS manifestations. Since majority of patients are alert and conscious, they usually complaints of the following symptoms.

Anxiety,

sleeplessness,

cephalgia,

giddiness,

blurring of vision,

depression,

increased tremulousness, and

other nonspecific complaints.

The conscious level of the patient can deteriorate in a rapid manner from confusion, lethargy to coma. The patients may show inappropriate behaviour. Convulsions can occur probably due to cholinergic toxicity.

Since both sympathetic and parasympathetic systems contain acetylcholine receptors the clinical features vary. Miosis is considered to be the most consistent sign. Increased bronchial secretion may mimic as pulmonary edema.(9)

Muscarinic cholinergic features may not be dramatic clinically. Because of sympathetic stimulation patient may have leucocytosis.(9) The same is the cause for hyperglycemia that can occur along with ketosis. This can

mimic ketoacidosis. Hypoglycaemia has also been reported but its mechanism is not known.(10)

Hyperglycemiamay be related to individual compound like malathion rather than whole of OPCs.(10)

Increased amylase levels may occur in OPC poisoning. Pancreatic edema may occur alone or in combination with pancreatitis in OPCs.(11)

This is common with malathion. Hepatic transaminases may also increase.(12)

CVS manifestations are an admixture of sympathetic and parasympathetic effects. Pulse rate may be normal, bradycardia or tachycardia can also occur. This poisoning may be associated with QT prolongation and life threatening arrhythmia.(13)

Hypotension can occur and can be troublesome in poisoning with high lipid soluble substance like dimethoate. If respiratory failure occur along with hypotension vasopressors may become mandatory. Such a scenario do not occur with other compounds.

Respirory system is affected in many ways. It is usually due to an interplay of following factors.

Increased bronchial secretions,

bronchoconstriction,

paralysis of intercostals and diaphragm, and

decreased central drive for respiration.

This will result in hypoxemia and ultimately in respiratory arrest which accounts for death in most circumstances. The first two factors will respond to atropine adequately but the later two will not. Securing the airway with intubation and mechanical ventilation may be needed to manage the situation. Aspiration pneumonitis can occur and patient may land up in ARDS.

ACh acts in neuromuscular junctions through nicotinic receptors. Its mechanism is similar to neuromuscular blockade by an depolarising agent which will lead to fasciculations and muscle weakness. This finding may not be seen even in severe poisonings sometimes.

Cranial nerve palsies are not common. Rarely nicotinic features alone occur in the absence of cholinergic features.

DELAYED COMPLICATIONS:

INTERMEDIATE SYNDROME:

Cardinal features of this syndrome are,

Delayed onset of muscle weakness,

Occurring after 24 to 96 hours of acute intoxication,

Resolution of cholinergic symptoms.

Clinically patients may have,

Weakness of proximal muscles particularly flexors of neck,

Cranial nerve involvement and

Respiratory muscle paralysis.

Patients are usually conscious unless they have pneumonia or hypoxic ischemic encephalopathy. As fatal respiratory arrest may occur early recognition of symptoms are crucial. Usually neck muscle weakness ie., difficulty in raising the head from the bed is the first sign.

The pathophysiology of this syndrome is largely unknown. Because of neuromuscular dysfunction, weakness of intercostals muscles and diaphragm will lead to respiratory failure. As consciousness is preserved in uncomplicated cases, lack of central respiratory drive is not a likely mechanism.

It is suggested that overstimulation of neuromuscular junction will ultimately result in down regulation of synaptic mechanisms(14). As repair of these processes may take long time, weakness may persist longer.

The incidence have predilection towards certain compounds like fenthion, parathion and malathion. Former has the highest reported incidence(15). Clinical recognition is the most reliable way to identify this syndrome(16).

Electromyogram in these patients will show “tetanic fade” suggestive of involvement of pre as well as post synaptic components.

Some studies suggest that intermediate syndrome may be attributed to “insufficient oxime therapy”(17). The management of this syndrome is mainly supportive in the form of mechanical ventilation and airway protection. Atropine or pralidoxime do not have substantial role in this syndrome except that they will be useful in treating cholinergic symptoms. Usually, resolution of paralysis and weakness may take several days from 5 to 18 days.

DELAYED NEUROPATHY:

Chronic exposures to OPCs may result in peripheral neuropathy. This may also occur several days after acute intoxication. “Organic phosphorus–induced delayed neuropathy (OPIDN)” occurs from the inhibition of the enzyme “neuropathy target esterase”.

This enzyme plays a major role in maintaining the phospholipid components of cell membrane and involved in cellular transport. Usually large fibres are affected which may reveal axonal degeneration pathologically.

Carbamates usually do not cause neuropathy except carbofuran which has been implicated in some cases. Some association between OPCs and parkinsonism has also been suggested.

BEHAVIORAL TOXICITY:

Acute as well as chronic exposure to OPCs can cause behavioural changes. Symptoms being,

confusion,

depression,

anxiety,

fatiguability,

irritability,

drowsiness and

psychosis.

Basal ganglia involvement has also been described.

DIAGNOSIS:

Diagnosis may be straight forward if the patients present with cholinergic crisis. As history may not be reliable in considerable number of cases, other diagnostic tests may be needed.

Treatment in acute poisoning should never be delayed till the confirmation of diagnosis.

The most appropriate tests are,

1)Measurement of specific OPCs and their metabolites in tissues

2)Cholinesterase activity in blood or plasma.

Unfortunately such assays may not be available within few hours of poisoning. Moreover standardised data describing “normal range” as well as “toxic concentrations” are not well established.

CHOLINESTERASE ACTIVITY:

The commonly measured cholinesterases are “butyryl cholinesterase (BuChE, plasma cholinesterase)” and red cell cholinesterase. BuChE is produced in liver. It is secreted into blood to metabolise xenobiotics. The latter is found in RBCs. Inhibition of these enzymes can serve as the marker of poisoning. But enzyme level in RBCs will predict AChE activity in neurons in acute poisoning(18).

After poisoning BuChE will be the first one to fall and followed by RBC enzyme. When patient is presenting with symptoms activity of both the enzymes will be significantly lower than baseline levels.

Levels of these enzymes at the time of admission may not correlate with the outcome.

RED CELL CHOLINESTERASE:

As stated previously enzyme activity in the RBCs may correlate with AChE levels in the neural tissue. When the RBC enzyme level is less than 30%, neuromuscular junction dysfunction occurs.(19) Its level can be correlated to hematocrit values.

If oximes are not used, the enzyme activity in the RBCs will reach normal levels after many weeks only. Its activity will also be reduced,in patients with,

perniciousanemia,

antidepressants, and

antimalarials.

For assessing enzyme activity, blood should be collected in appropriate collecting tubes, if they contain fluoride, it will inactivate the enzymes permanently resulting in false low values.

It must contain anticoagulant, EDTA to assess RBC enzyme activity not for BuChE.

ATROPINE CHALLENGE:

This can be used when history is not available or reliable in the setting of suspected OPC poisoning. Atropine in a dose of 1 mg in adults and 0.05 mg/kg in children will produce antimuscarinic symptoms like mydriasis, tachycardia, and or dry mucous membranes in an unexposed individual. If cholinergic symptoms persist even after atropine injection, it strongly suggests OPC poisoning.

ELECTROMYOGRAM:

"Spontaneous repetitive potentials or fasciculations followingsingle nerve stimulation resulting from persistent acetylcholine at nerve terminals" can be used as a reliable indicator of early OPC poisoning.

DIFFERENTIAL DIAGNOSIS:

This may include following

1)Anticholinesterase medicines like

neostigmine,

physostigmine,

pyridostigmineand

echothiophate iodide.

2)Cholinomimetics like

Pilocarpine,

Carbachol,

Aceclidine,

Bethanechol,

Methacholine

3)Nicotine Alkaloids like

Coniine,

Lobeline, and

Nicotine

4)Carbamate insecticides

5)muscarine-containing mushrooms

MANAGEMENT

Important components of managing OPC poisoning are,

1)protection of airway and if needed mechanical ventilation

2)stabilisation of cardiorespiratory systems

3)control of seizures

Protection of airway can be ensured by endotracheal intubation early and mechanical ventilation particularly positivepressure ventilation in unconscious patients, in significantly weak muscle power, and in patients who cannot handle increased secretions.

ANTIMUSCARINIC THERAPY:

Simultaneous management of cholinergic crisis is an integral part of patient care since it will reduce respiratory secretions and improve oxygenation.

Atropine is a competitive muscarinic receptor antagonist which counteracts,

increased secretions,

pupillary constriction,

bronchospasm,

loose stools,

vomiting,

sweating and

bladder continence.

Intravenous atropine in the dose of 1 to 3mg according to the severity of poisoning in adults and in children at a dose of 0.05mg/kg upto adult dose depending upon the response.

Atropinisation:

Patient is said to have atropinised if he has following features.

Dry mucous membranes,

absent or decreased bowel sounds,

increased pulse rate,

decreased oral and respiratory secretions,

no bronchospasm and

pupillary dilatation.

Since major cause of mortality is cardiorespiratory failure, its function should guide the management rather than pupil size or wet skin. Target of atropine therapy is to have a BP of 90 mm of Hg systole, a pulse rate of atleast 80/mt and a clear lungs.

Once atropinisation is achieved patients can be maintained with atropine infusion upto 2mg/hr and in children at a dose of 0.025mg/kg/hr.

Complete absence of bowel sounds,

severe tachycardia,

mydriasis and

bladder retention

allcan be the signs of “overatropinisation” which can be detrimental because of hyperthermia and atropine induced delirium.

However tachycardia may have multiple causes like

dehydration,

aspiration pneumonitis and

delirium.

High doses of atropine may be needed to counteract

bronchospasm,

increased secretions and

bradycardia.

Some heavily poisoned individuals required even upto 1 gram of atropine in 24 hrs.

Atropine cannot reverse the nicotinic side effects of OPC poisoning. So patients should be monitored for skeletal muscle weakness of proximal group particularly neck muscle weakness.

Once identified, patients should be observed for respiratory distress and promptly intubated. Mechanical ventilation should be initiated according to the need.

If patients develop CNS toxicity due to atropine and there are signs of peripheral cholinergic signs like

bronchorrhoea,

vomiting or

bradycardia

glycopyrrolate can be substituted for atropine.

This is equally efficacious and safe.(20) Like atropine, large doses of glycopyrrolate may be required in severe intoxication.

OXIMES:

OPCs phosphorylate the AChE enzyme, active form of enzyme can be regenerated by hydrolysis. This slow process can be accelerated to many folds by administration of oximes like obidoxime or pralidoxime chloride.(21) This will mitigate the nicotinic as well as muscarinic features.

Oximes can be useful even if they are administered late in the course of poisoning particularly in fat soluble OPCs. As a rule they should be given as early as possible.

Side effects include

vomiting,

diastolic hypertension,

neuromuscular blockadeand

visual disturbances.

DIAZEPAM:

Diazepam administered with oximes decrease incidence of seizures and improve survival and neuropathy(22). It can also reduce brain damage from OPC related seizures.

Phenytoin is ineffective in toxin induced seizures. Diazepam is not recommended in all cases of OPC poisoning.

DECONTAMINATION:

All the clothing should be removed in order to decrease cutaneous absorption. Medical personnel should wear double gloves and protective apron. Skin must be triple washed with water and soap. Skin soiled with contaminated vomitus and stools can absorb the poison and should be washed

thoroughly.Stomach wash should be given in all patients unless contraindicated.

POTASSIUM:

Potassium is an important intracellular ion required for many vital cellular functions. If its serum concentrations are altered, serious clinical manifestations can occur. 70 to 150 mmol of potassium is present in a typical western diet daily. Its levels are maintained between 3.5 to 5 mM.

DISTRIBUTION:

After being absorbed from GIT, potassium is dietributed mainly into intracellular compartment where it is the major cation and also into ECF. Its concentration is about 100 to 120 mmol/l in the cytoplasm.

Total potassium content in ithe ICF compartment in a healthy adult is about 3000 to 3500 mmol. Majority (70%) of which is present in muscles and the remaining in bone, skin, RBCs and liver.

Only upto 2% of potassium is present in ECF. It is produced by the action of Na+,K+-ATPase pump which is present in almost all the cells. This pump transports three sodium ions extracellularly in exchange for 2 potassium ions intracellularly.

Membrane potential is mainly determined by this differential distribution of these cations which leads to development of a more electronegative intracellular compartment.

This electric potential is mandatory in neural function and contraction of muscles.

Serum levels of this cation is tightly regulated by various mechanisms. A “feed forward” system is said to exist in GIT or portal sensors for potassium which helps in renal excretion of potassium by the mechanisms independent of serum aldosterone or potassium levels(23).

This reflex mechanism aids the kidney to balance between daily intake and daily excretion of potassium through kidneys.

Factors maintaining the distribution of potassium can be divided into

those decreasing its levels and

those increasing its levels.

Serum levels are decreased by,

insulin,

beta agonists,

alkalosis and

alpha blockers.

Serum levels are increased by

acidosis,

hyperglycemia,

beta blockers,

alpha agonists,

hyperosmolality and

exercise.

Acidosis caused by inorganic anions like NH4Cl or HCl will produce hyperkalemia by unknown mechanisms. But organic anions usually do not produce such an effect. Beta2 agonists and insulin activate Na+,K+-ATPase and thereby shifts potassium intracellularly.

Activation of Beta2 receptor will increase the intracellular cAMPwhich in turn stimulate Na+,K+-ATPase pump. Alpha receptor activation has the opposite effect.

ALDOSTERONE:

By 2 major mechanisms this hormone reduces serum potassium.

1) It causes redistribution of potassium intracellularly.

2) It enhances renal excretion of potassium & to a minor extent in GIT.

HYPEROSMOLALITY:

Hyperosmolality drives water out of the cells, intracellular potassium conaentration rises. This inhibits Na+,K+-ATPase pump and intracellular levels are normalised. This can occur only with “effective osmoles” as it occurs in hyperglycemia in diabetic patients or with administration of mannitol. If hyperglycemia occurs in non diabetics in whom endogenous insulin is normal, it will enhance insulin secretion leading to hypokalemia.

EXERCISE:

Exercise will cause alpha receptor activation resulting in hyperkalemia which will cause dilatation of arteries leading to increased blood flow to skeletal muscles. Simultaneous beta receptor activation will reduce its severity but same can lead to hypokalemia following exercise.

If severe hypokalemia occurs in susceptible individuals it can lead to rhabdomyolysis.

RENAL HANDLING OF POTASSIUM:

Potassium homeostasis on long term basis is effected through kidneys. This occurs almost exclusively in the collecting duct. Since potassium is not protein bound, it is freely filtered across the glomerulus.

About 60 to 70% is reabsorbed in the proximal convoluted tubule. A

modest net reabsorption occurs in “loop of henle”. This can be altered by a loop diuretic.

Potassium excretion is principally regulated in distal collecting duct and tubules active secretion combined with reabsorption. Cortical collecting duct possess the principal collecting duct which contains “apical sodium channel (ENaC)”. This channel reabsorbs sodium which activates Na+,K+-ATPase in the basolateral membrane. So intracellular potassium levels rise.

This potassium is secreted into luminal fluid by KClcotransporters and apical potassium channels. Potassium reabsorption occurs by the “apical H+,K+-ATPase” in the intercalated cells. This secretes H+ ions back to the luminal fluid. These 2 different processes ensure effective control of potassium through kidneys.

Potassium secretion by the principal cells are tegulated by,

flow rate of luminal fluid,

sodium delivery to the distal tubules,

serum aldosterone,

potassium in ECF, and

pH of ECF

in the decreasing order of significance.

If “luminal flow rate” increases, it will reduce intraluminal potassium levels. This will increase concentration gradient for potassium across “apical membrane”. This will result in potassium secretion.

Secondly it directly stimulates potassium secretion by altering apical membrane potassium gradient.

DIURETICS:

So if flow rate decreases hyperkalemia occurs. If reabsorption of sodium decreases, forces driving potassium secretion also decreases and hyperkalemia occurs. This how “Potassium-sparing diuretics,” act. They decrease sodium reabsorption either directly or indirectly.

Thiazide and loop diuretics increase sodium delivery to the distal collecting ducts and enhance sodium absorption and hyperkalemiamay occur.

ALDOSTERONE:

Aldosterone has many effects on potassium secretion by principal cells. It increases expression of Na+,K+-ATPase and “apical sodium channel (ENaC)”. This will lead to increased potassium secretion.

ACIDOSIS:

Metabolic acidosis directly affect potassium channels and interstitial ammonia concentration thereby decreases potassium secretion. Respiratory acidosis has minimum influence on potassium secretion.

Activity of “apical H+,K+-ATPase” is altered by

potassium levels,

pH, and

aldosterone.

Hypokalemia increases expression of H+,K+-ATPase leading to increased potassium absorption and reduced secretion. Aldosterone also increases expression of H+,K+-ATPase, and alleviate potassium secretion. Metabolic acidosis also affect H+,K+-ATPase activity and contribute to the development of hyperkalemia.

CHRONIC KIDNEY DISEASE (CKD) AND POTASSIUM HANDLING:

Potassium balance can be maintained to near normal levels until GFR falls substantially. This is because compensatory increase in potassium excretion by individual nephron. But CKD patients cannot handle an acute load of potassium effectively because of decreased functioning nephrons and limitations of compensatory mechanisms.

Drugs causing hyperkalemia like ARBs, ACEIs, and beta blockers have profound effect in CKD patients.

HYPERKALEMIA:

It is defined as serum potassium level of 5.5 meq/dl. When it is more than 6Mm, it can be fatal.

CAUSES:

"Pseudo hyperkalemia" as occurs in

- Hemolysis in vitro,
- RBC membrane transport defects

Extra cellular potassium shift as occurs in

- Acidosis
- Hyperosmolality due to mannitol or radiocntrasts
- Beta blockers
- Digoxin
- "hyperkalemic periodic paralysis"
- Rapid lysis of tumor cells
- Amino acids like arginine and lysine

Decreased excretion of potassium as occurs due to drugs like,

Aliskiren a renin inhibitor,

ACE inhibitors,

Succinyl choline,

Aldosterone antagonists

Angiotensin receptor blockers,

“potassium sparing diuretics”

Trimethoprim,

Nafamostat, and

Pentamidine,

Decreasd delivery of potassium to tubules as occurs in

Hypovolemia

Heart failure

Disuse atrophy

Chronic kidney disease

Acute oliguric renal failure

HYPOKALEMIA:

Hypokalemia is defined as serum levels less than 3.6 mM.If renal functions are normal and patients are not on medications, less than 1% of population will develop either hypokalemia or hyperkalemia.

So in the absence of drugs, occurance of either condition in a healthy adult should lead to suspicion of an underlying disease. But hypokalemia usually occurs with drugs or specific diseases such as patients on diuretics.

CLINICAL MANIFESTATIONS:

Hypokalemia can affect

nerves,

blood vessels and heart,

gut,

muscles and kidney. Elderly individuals do not tolerate hypokalemia

unlike their younger counterparts.

CARDIOVASCULAR SYSTEM:

Low potassium diet is associated with an increased prevalence of systemic hypertension. Potassium supplementation will reduce BP. Hypokalemia may cause sodium retention and lead to hypertension.

Fatal arrythmias like ventricular fibrillation can occur in hypokalemia. Risk of sudden cardiac death is high.

HORMONAL:

Hypokalemia will reduce insulin secretion and precipitate insulin resistance leads worsening of glycemic status and diabetic control(24).

Thiazide induced hyperuricemia and hypokalemia may cause endothelial dysfunction and contribute to insulin resistance observed in patients on thiazide diuretics.

SKELETAL MUSCLES:

Because hypokalemia causes hyperpolarisation of cells of skeletal muscles, muscle contraction will be impaired. Hypokalemia reduces blood flow to skeletal muscles. Severe hypokalemia may cause rhabdomyolysis following exercise.

KIDNEYS:

Effects comprise of

reduced blood flow to medullary region,

increased resistance in renal vasculature,

cystic and tubulo interstitial changes,

pH alteration, and

retarded concentrating mechanisms of kidneys.

CYSTIC AND TUBULO INTERSTITIAL CHANGES:

Hypokalemia causes interstitial fibrosis particularly outer medulla. Even it is reversible, sometimes it may cause ranal failure. Hypokalemia can cause hypertrophy of renal parenchyma and may predispose to the development of renal cysts.

ACID-BASE DISTURBANCE:

Hypokalemia will cause metabolic alkalosis due to increased secretion of H+ ions. This may lead to a viscous cycle. If respiratory failure occurs because of hypokalemia it can result in respiratory acidosis.

CONCENTRATION DEFECTS:

Hypokalemia impairs concentrating mechanisms of kidneys leading to mild polyurea about 2-3 L/day.

HEPATIC ENCEPHALOPATHY:

Hypokalemia increases ammonia production in the kidneys. Nearly 50% of this can enter systemic circulation and hepatic encephalopathy may worsen.

ETIOLOGY:

Etiology of hypokalemia can be divided into 4 classes.

1) Nonrenal potassium losses
2) potassium losses through kidneys
3) redistribution
4) Pseudohypokalemia

PSEUDOHYPOKALEMIA:

This condition is due to an artefact not true hypokalemia like that occurs after phlebotomy. AML is the most common condition associated with this. Large numbers of tumour cells take up K+ intracellularly if blood is stored at room temperature for long time.

REDISTRIBUTION:

As previously mentioned hormones will influence the shift of potassium between ECF and ICF.

NONRENAL LOSSES OF POTASSIUM:

GIT and skin usually excrete small amounts of K+ daily. Occasionally, chronic diarrhoea or excessive sweating causes significant potassium loss(25).

RENAL LOSSES:

the most common etiology.

Medicines:

Both loop diuretics and thiazide increase urinary K+excretion and adjusted for their dieresis, thiazides commonly causes hypokalemia. Penicillin analogues, like carbenicillin, increases urinary K+ excretion.

AmphotericinB increases collecting duct K+ secretion directly. Cisplatinmay induce hypokalemia.

Hormones:

As stated previously aldosterone causes renal loss of K+.

Deficiency of Magnesium:

Magnesium depletion can cause severe hypokalemia particularly in the setting of diuretic therapy. This should be suspected if K+ replacement does not correct the K+ loss.

Intrinsic Renal Mechanisms:

These conditions are rare. Bartter syndrome will have

normal or low BP,

metabolic alkalosis,

hypercalciuria and

hyperreninemia.

Gitelman'ssyndrome will have same features except hypercalciuriainstead it will have hypocalciuria.

Liddle syndrome will have

hypokalemia,

severe systemic hypertension,

hyporeninemia and

decreasedaldosterone levels.

Bicarbonaturia:

Bicarbonaturia may occur because of

distal RTA(renaltubular acidosis),

metabolic alkalosis, or

in the treatment of proximal RTA(renal tubular acidosis).

“HYPOKALEMIC PERIODIC PARALYSIS (HYPOKPP)”

Onset of “HypoKPP” occurs during adolescence. This disease is more common in men than women. If “episodic weakness” occurs after the age of 25 years HypoKPP can almost be ruled out.

High carbohydrate or sodium diet will provoke attacks of weakness which proximal rather than the distal muscles of limbs. Involvement of cranial nerves is not common. It may be fatal if respiratory muscles are involved though these are usually not affected.

Cardiac arrhythmias may be deadly if hypokalemia is severe. “Thyrotoxic periodic paralysis” will mimic HypoKPP. But this condition will improve after the treatment with anti thyroid drugs. Hypokalemia during the attacks of weakness in the abscence of other causes will establish the diagnosis. EMG may show reduction in amplitude, and in severely weak muscles even electrical silence.

TREATMENT:

Oral potassium chloride in the dose of 0.2 to 0.4 mmol/kg can be given in the interval of 30 minutes. Intra venous treatment is needed only rarely in which case mannitol is preferred. Diets rich in carbohydrate and sodium should be avoided. Acetazolamide in a dose of 125 to 1000 mg, 25 to 100 mg of triamterene, or 25 to 100 mg of spironolactone may used as a prophylaxis.

DIAGNOSIS:

redistribution or pseudohypokalemia should be excluded first. The above said four categories should be looked for. If diuretic therapy or metabolic alkalosis is the cause, they will cause urinary loss of K+. Hypomagnesemia as a result of diuretic therapy, will cause hypokalemia which is refractory to treatment.

Diagnostic workup can be explained as follows.

Step1. Is there an abnormal leucocytes present?

If yes, pseudohypokalemia may be suspected and it should be confirmed by rapid separation of plasma or storing blood at 4 degree C.

If leucocytes are normal, move to the next step.

Step 2. Is there evidence for recent insulin, elevated aldosterone,

adrenergic drugs, or theophylline?

If yes, hypokalemia is due to redistribution.

If there is no such evidence, move to further workup.

Step 3. Is there any fluid loss from skin or GIT?

If yes, hypokalemia is due to non renal loss. If it is not,

Step 4. Assess urinary potassium levels.

If 24 hours urinary excertion is less than 20 mmol/day then hypokalemia may be due to poor oral intake, recent diuretic use or recent GI loss.

Step 5. If potassium excretion is more than 20 mmol/day, two scenarios can be suspected

Scenario 1.hypokalemia may be due to

Drugs like diuretics, amphotericin or aminoglycosides.

Or it is due to bicorbanaturia orHypomagnesemia.

Scenario 2. Assess BP

If it is low,Bartter or Gitelman syndrome should be considered.

If BP is high, assess plasmaaldosterone and cortisol.

If aldosterone is low with normal cortisol, liddle syndrome is the possibility.

If aldosterone is normal or low with increased cortisol, cushing'ssyndrome should be suspected.

If aldosterone is high with normal cortisol, hyperaldosteronism should beconsidered.

TREATMENT:

The risks of treatment should be balanced against the risk of hypokalemia. Treatment induced hyperkalemia may cause fatal “ventricular tachycardia or fibrillation”.

The absolute indications are,

1)“hypokalemic periodic paralysis (hypoKPP)”

2)Patients with severe hypokalemia needing urgent surgery

3)Ventricularectopics in the setting of acute coronary syndrome.

In such scenarios, intra venous KCl in a dose of 5-10mmol over 15-20 minutes can be given an may be repeated as needed. ECG must be closely monitored.

Whenever possible, KCl for chronic hypokalemia must be given orally. For IV therapy, 10 mmol/hour will be a safe dose. Dextrose containing solutions will aggrevate hypokalemia because it stimulates secretion of insulin.

Treatment of underlying disease is essential. In cases of refractory hypokalemia, hypomagnesemia should suspected and treated if present.

HYPOKALEMIA IN THE SETTING OF OPC POISONING:

Hypokalemia is a common finding in OPC poisoning(26). Exact mechanisms by which hypokalemia occurs is not known. Proposed

mechanisms include, excessive vomiting, ganglionic stimulation related sympathetic overactivity, andhypomagnesemia. None of these mechanisms are proved. So far no randomised control trial has been conducted to assess hypokalemia in this setting. Only a few case reports are available.

When hypokalemia complicates this poisoning, it may interfere with neuromuscular synaptic functions which are already compromised because poisoning. It can induce cardiac rhythm abnormality which can adversely affect the outcome.(27)

MATERIAL AND METHODS

SETTING:

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital and Madras Medical College.

ETHICS COMMITTEE APPROVAL:

Obtained.

STUDY DURATION:

This study was conducted over a period of six months.

STUDY POPULATION:

Patients admitted with history of organophosphorus compound poisoning in toxicology ward, Institute of Internal medicine.

SAMPLE SIZE:

Fifty cases admitted with history of organophosphorus compound poisoning.

TYPE OF STUDY:

Cross sectional study

INCLUSION CRITERION:

Patients admitted with history of organophosphorus compound poisoning.

EXCLUSION CRITERIA:

Known kidney disease patients,

heart disease patients,

patients on diuretics.

DATA COLLECTION AND METHODS

- Informed consent was obtained from each patient or the relative.
- Patients had their history taken according to a Questionnaire and were subjected to clinical examination.
- Renal function tests were done in all patients.
- All the data were entered in the proforma(enclosed).
- SPSS package and ANOVA was used to analyse the data.

OBSERVATION AND RESULTS

AGE AND HYPOKALEMIA

	Serum potassium levels meq/dl	N	Mean	Std. Deviation	Std. Error Mean
Age in years	Hypokalemia	24	38.38	14.111	2.880
	Normal	26	34.12	13.364	2.621

INDEPENDENT SAMPLES TEST

		Levene's Test for Equality of Variances		t-test for Equality of Means							P VALUE
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference		
									Lower	Upper	
Age in years	Equal variances assumed	2.048	.159	1.096	48	.278	4.26	3.886	-3.553	12.072	.278
	Equal variances not assumed			1.094	47.129	.280	4.26	3.894	-3.574	12.093	

SEX AND SERUM POTASSIUM LEVELS

			Serum potassium levels meq/dl		
			Hypokalemia	Normal	Total
Sex					
	Male	Count	20	19	39
		% within Sex	51.3%	48.7%	100.0%
		% within Serum potassium levels meq/dl	83.3%	73.1%	78.0%
	Female	Count	4	7	11
		% within Sex	36.4%	63.6%	100.0%
% within Serum potassium levels meq/dl		16.7%	26.9%	22.0%	

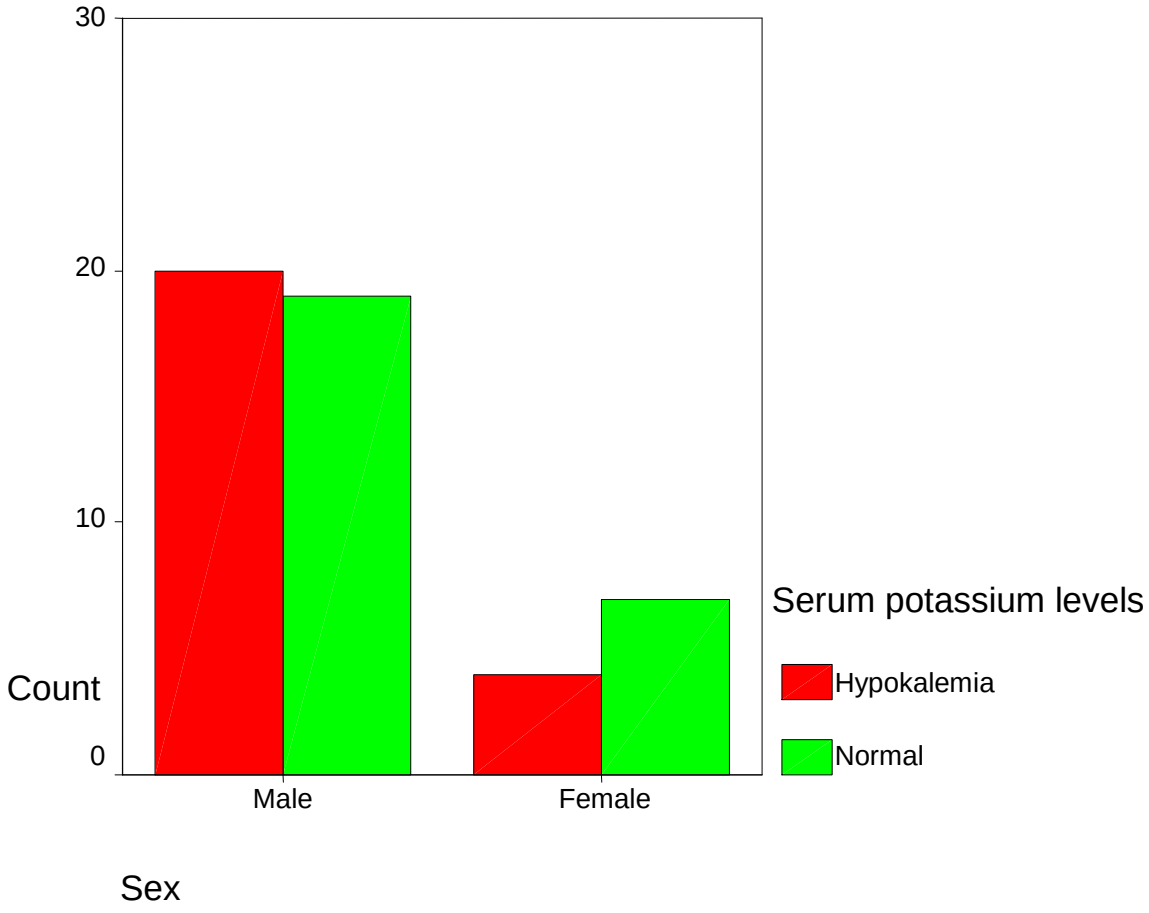
Total	Count	24	26	50
	% within Sex	48.0%	52.0%	100.0%
	% within Serum potassium levels meq/dl	100.0%	100.0%	100.0%

CHI-SQUARE TESTS

SEX AND SERUM POTASSIUM LEVELS

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	P value
Pearson Chi-Square	.765(b)	1	.382			
Continuity Correction(a)	.284	1	.594			
Likelihood Ratio	.774	1	.379			.382
Fisher's Exact Test				.501	.298	
Linear-by-Linear Association	.750	1	.387			
N of Valid Cases	50					

SEX AND SERUM POTASSIUM LEVELS



SERUM POTASSIUM LEVELS (MEQ/DL) AND OUTCOME

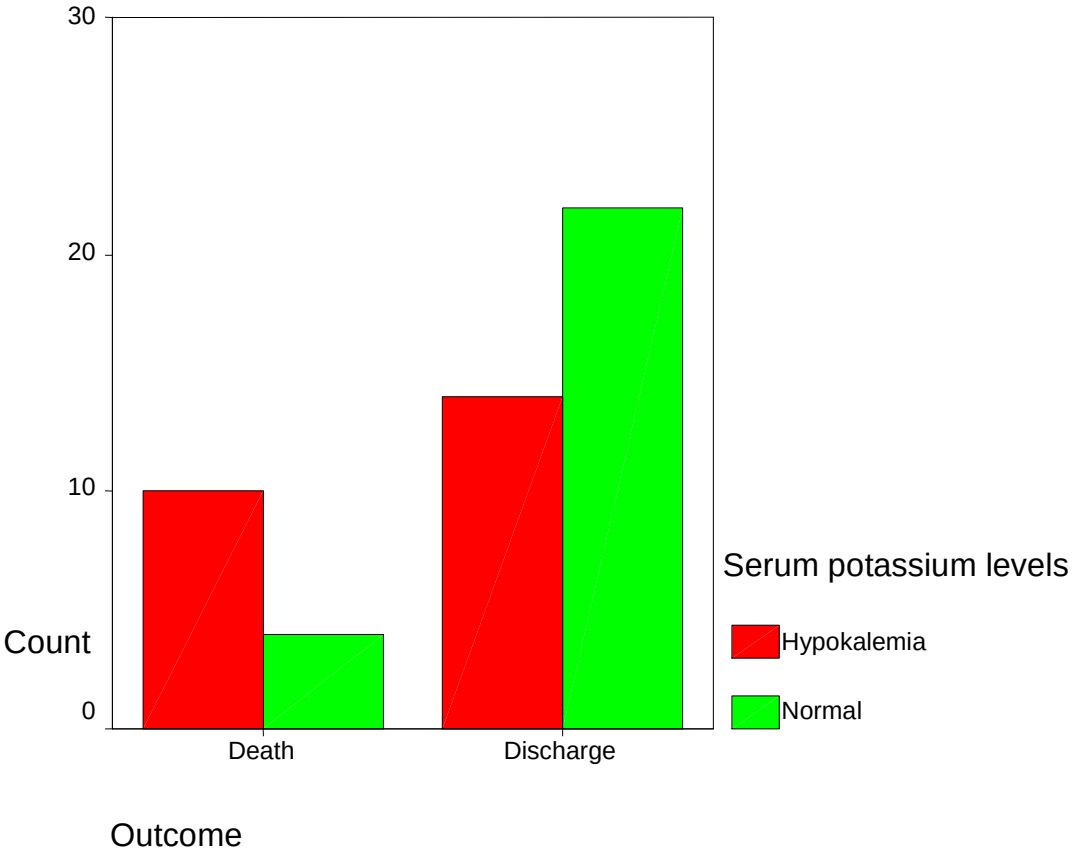
			Serum potassium levels meq/dl		
			Hypokalemia	Normal	Total
Outcome					
	Death	Count	10	4	14
		% within Outcome	71.4%	28.6%	100.0%
		% within Serum potassium levels meq/dl	41.7%	15.4%	28.0%
	Discharge	Count	14	22	36
		% within Outcome	38.9%	61.1%	100.0%
% within Serum potassium levels meq/dl		58.3%	84.6%	72.0%	
Total		Count	24	26	50
			48.0%	52.0%	100.0%

		% within Outcome			
		% within Serum potassium levels meq/dl	100.0%	100.0%	100.0%

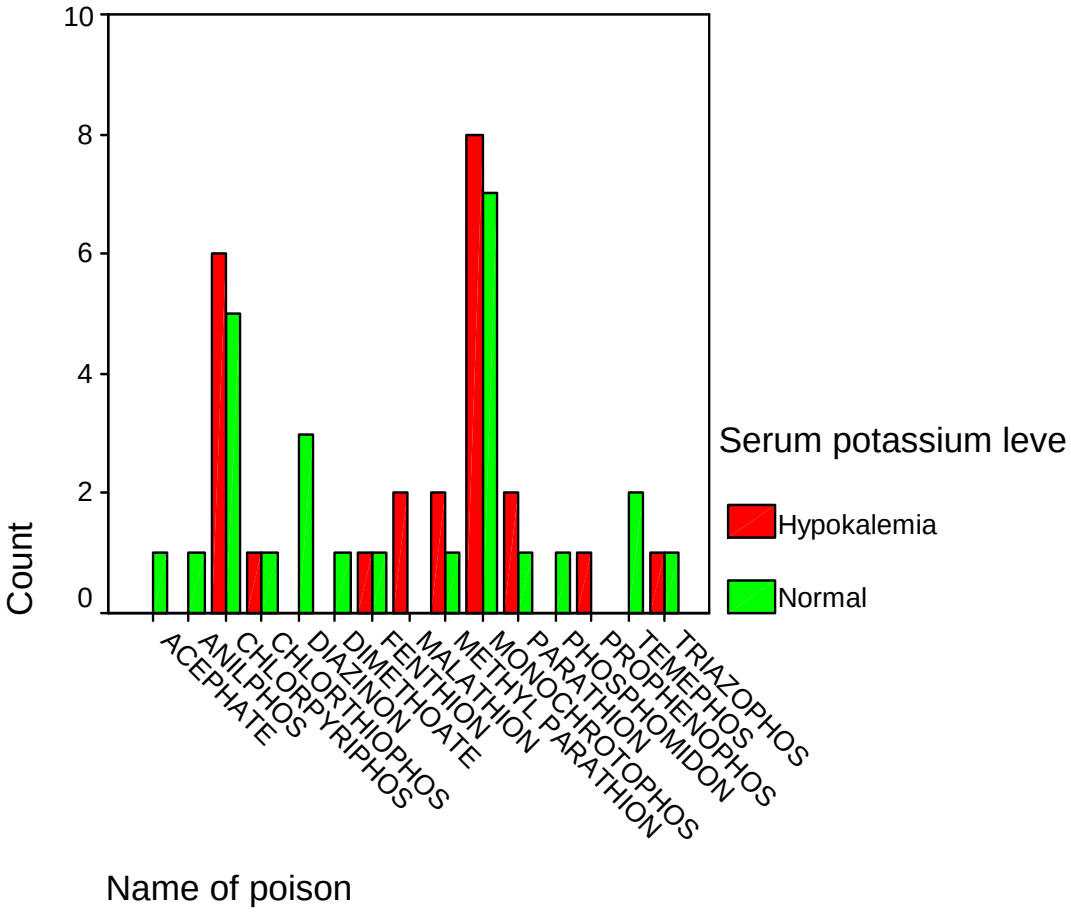
CHI-SQUARE TESTS

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	P value
Pearson Chi-Square	4.276(b)	1	.039			
Continuity Correction(a)	3.072	1	.080			
Likelihood Ratio	4.369	1	.037			.039
Fisher's Exact Test				.059	.039	
Linear-by-Linear Association	4.191	1	.041			
N of Valid Cases	50					

SERUM POTASSIUM LEVELS (MEQ/DL) AND OUTCOME



INDIVIDUAL POISON AND POTASSIUM LEVELS



CHI-SQUARE TESTS

	Value	df	Asymp. Sig. (2-sided)	P value
Pearson Chi-Square	12.765(a)	14	.545	.545
Likelihood Ratio	17.393	14	.236	
N of Valid Cases	50			

SERUM SODIUM LEVELS(meq/dl) AND SERUM POTASSIUM LEVELS(meq/dl)

			Serum potassium levels meq/dl		
			Hypokalemia	Normal	Total
Serum sodium level meq/dl					
	< 135	Count	6	8	14
		% within Serum sodium level meq/dl	42.9%	57.1%	100.0%
		% within Serum potassium levels meq/dl	25.0%	30.8%	28.0%
	> 135	Count	18	18	36
		% within	50.0%	50.0%	100.0%

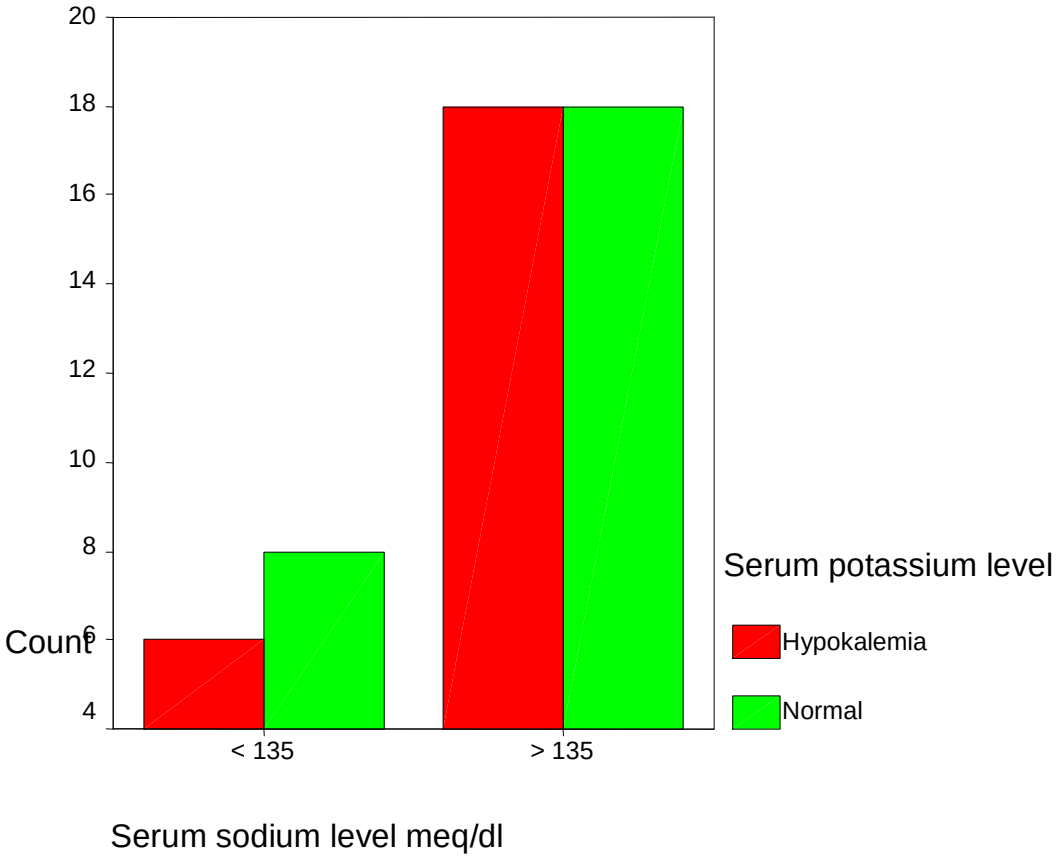
		Serum sodium level meq/dl			
% within Serum potassium levels meq/dl		75.0%	69.2%	72.0%	
Total		Count	24	26	50
		% within Serum sodium level meq/dl	48.0%	52.0%	100.0%
		% within Serum potassium levels meq/dl	100.0%	100.0%	100.0%

CHI-SQUARE TESTS

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	P value
Pearson Chi-Square	.206(b)	1	.650			
Continuity Correction(a)	.019	1	.890			.650
Likelihood Ratio	.207	1	.649			
Fisher's Exact Test				.757	.446	
Linear-by-Linear Association	.202	1	.653			
N of Valid Cases	50					

SERUM SODIUM LEVELS(meq/dl) AND SERUM POTASSIUM

LEVELS(meq/dl)



SERUM POTASSIUM LEVELS AND DURATION OF HOSPITAL STAY(IN DAYS)

	Serum potassium levels meq/dl		ean	S td. Deviation	td. Error Mean
Duratio n of hospital stay in days	Hypoka lemia	4	.29	3. 014	615
	Normal	6	.08	2. 992	587

INDEPENDENT SAMPLES TEST

		Levene's Test for Equality of Variances		t-test for Equality of Means							P value
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference		
									Lower	Upper	
Duration of hospital stay days	Equal variances assumed	.114	.738	.253	48	.802	.21	.850	-1.494	1.924	.802
	Equal variances not assumed			.253	47.623	.802	.21	.850	-1.495	1.925	

SERUM POTASSIUM LEVELS AND DURATION OF MECHANICAL

VENTILATION (IN DAYS)

	Serum potassium levels meq/dl	N	Mean	Std. Deviation	Std. Error Mean
Duration of mechanical ventilation days	Hypokalemia	24	2.79	2.449	.500
	Normal	26	1.42	2.062	.404

INDEPENDENT SAMPLES TEST

		Levene's Test for Equality of Variances		t-test for Equality of Means							P value
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference		
									Lower	Upper	
Duration of mechanical ventilation days	Equal variances assumed	.249	.620	2.143	48	.037	1.37	.639	.085	2.653	.037
	Equal variances not assumed			2.128	45.163	.039	1.37	.643	.074	2.664	

RESULTS

AGE:

Of 50 patients studied, 24 patients had hypokalemia(serum potassium levels <3.6meq/dl) and 26 had normal serum potassium levels. The mean age for patients with hypokalemia was 38.38 and mean age for other was 34.12. This difference was statistically not significant(p value- 0.278)

SEX:

In this study, totally 24 patients had hypokalemia. Of 39 male patients, 20 patients (51.3%) had hypokalemia. Of 11 female patients, 4 patients(36.4%) had hypokalemia. This difference of 14.9% of increased incidence in male patients was not statistically significant.(p value0.382).

MORTALITY:

During the study period, totally 14 deaths occurred. Among this 10 patients had hypokalemia which accounts for 71.4% and the remaining 4 patients had, normal serum potassium levels which accounts for, 28.6% and it is statistically significant(p value- 0.39).

INDIVIDUAL POISON AND POTASSIUM LEVELS:

In this study, totally 15 different poisons were involved. Of 24 cases of hypokalemia, monochrotophos is responsible for maximum number of cases being involved in 8 cases followed by chlorpyriphos in 6 cases.Acephate, anilphos, diazinon, dimethoate, phosphomidon, and temephos did not cause hypokalemia in any cases. However this increased incidence with individual poisons are not statistically significant(p value- 0.545).

SERUM SODIUM LEVELS AND SERUM POTASSIUM LEVELS:

Of 50 patients totally, 14 had hyponatremia(<135 meq/dl) which constitutes 28%. Of this 6 patients had hypokalemia which accounts for 42.9% of hyponatremia. Of 24 patients with hypokalemia this 6 cases of hyponatremia accounts for 25%. This association is not significant statistically (p value- 0.650). Hypernatremia did not occur in any patient.

SERUM POTASSIUM LEVELS AND DURATION OF HOSPITAL STAY:

In the current study mean duration of hospital stay in hypokalemia patients was 6.29 days, whereas in patients with normal potassium was 6.08 days. Hypokalemia did not prolong hospital stay. (p value- 0.802).

SERUM POTASSIUM LEVELS AND DURATION OF MECHANICAL VENTILATION:

Out of 50 patients, 28 patients needed mechanical ventilation.

All 14 patients who died had required mechanical ventilation. Of 28 patients needed mechanical ventilation, 18 patients had hypokalemia.

The mean duration of mechanical ventilation in hypokalemia patients was 2.79 days which is almost double as the mean duration in patients with normal potassium which was 1.42 days. This prolongation in mechanical ventilation was statistically significant (p value- 0.037).

DISCUSSION

NUMBER OF PATIENTS:

Name of the study	Number of patients:
D.R.Mahadeshwara Prasad et al	50
Lyzhnikov EA et al	73
Current study	50

In D.R.Mahadeshwara Prasad et al study, the author studied relationship between serum potassium levels with muscle twichings& fasciculations, respiratory distress, mortality and convulsions in 50 patients.

In Lyzhnikov EA et al study, the relationship between plasma and RBC levels of potassium and sodium with mortality and ECG was analysed in 73 patients with OPC poisoning.

AGE:

Mean age of the patients in D.R.Mahadeshwara Prasad et al study was27.14 years. In current study mean age for patients with normal potassium was 34.12 years and for patients with hypokalemia was 38.38 years.. In Lyzhnikov EA et al Study age difference was not studied.

GENDER:

In D.R.Mahadeshwara Prasad et al study and Lyzhnikov EA et al Study the significance of gender and hypokalemia was not studied. In the current study, of 24 patients with hypokalemia, 20 were male patients and 4 were female patients.

MORTALITY:

In Lyzhnikov EA et al Study, severe arrhythmia and cardiac arrest leadind to death occurred in 29 patients who are found to have hypernatremia and hypokalemia. In D.R.Mahadeshwara Prasad et al study, death occurred in patients with a mean potassium levels of 2.90 +/- 0.057 meq/dl(p value < 0.001). In the current study, out of 14 deaths totally, 10 patients(71.4%) had hypokalemia .

INDIVIDUAL POISON AND POTASSIUM LEVELS:

In Lyzhnikov EA et al Study, patients had poisoning with chlorophos, carbophos ,and thiophos. In D.R.Mahadeshwara Prasad et al study, significance to individual poison was not analysed. In the current study there is no statistically significant association between an individual poison and hypokalemia.

SERUM POTASSIUM AND SERUM SODIUM LEVELS:

In the current study, 14 patients had hyponatremia(<135 meq/dl).

Of which, 6(41.6%) had hypokalemia but this was not significant statistically.(p value-0.650) None of the patients had hypernatremia. In D.R.Mahadeshwara Prasad et al study sodium disturbance was not studied. In Lyzhnikov EA et al Study, hypernatremia was associated with hypokalemia and icreased mortality.

SERUM POTASSIUM LEVELS AND DURATION OF HOSPITAL STAY:

In the current study mean duration of hospital stay in hypokalemia patients was 6.29 days, whereas in patients with normal potassium was 6.08 days. Hypokalemia did not prolong hospital stay.(p value-0.802).

In both previously done studies, duration of hospital stay was not assessed.

SERUM POTASSIUM LEVELS AND DURATION OF MECHANICAL VENTILATION:

In D.R.Mahadeshwara Prasad et al study, both respiratory distress and mechanical ventilation taken together and statistically significant(p value < 0.001). In the current study, mean duration of mechanical ventilation was prolonged(p value-0.037). In Lyzhnikov EAet alStudy, mechanical ventilation was not assessed.

LIMITATIONS OF THE STUDY

- Because there is no randomisation, the influence of confounding factors like infection, and development of multi organ dysfunction cannot be eliminated.

- As included in the criteria, patients with renal failure have been excluded. So electrolyte disturbance in this population cannot be assessed.

- Number of female patients in the study group is small.

CONCLUSION

- Hypokalemia increases both morbidity and mortality in organophosphorus compound poisoning significantly.

- Hypokalemia can be used as a reliable and a cost effective marker of morbidity and mortality in organophosphorus compound poisoning.

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PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY :

TREATMENT HISTORY :

DRUG ALLERGY :

GENERAL EXAMINATION :

VITALS :

SYSTEMIC EXAMINATION :

CARDIOVASCULAR SYSTEM :

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM :

SERUM POTASSIUM :

RENAL FUNCTION TESTS :

PATIENT CONSENT FORM

Study Detail : HYPOKALEMIA IN ORGANOPHOSPHOROUS COMPOUND POISONING

Study Centre : Institute of internal medicine,, Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above ❑

study.

I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination , biochemical, immunological test. ❑

Signature of Investigator

Signature/thumb impression

Study Investigator's Name:

Patient's Name and Address:

Dr.MARIRAJ.I.,

MASTER CHART

Serial no	Sex	Age	Name of poison	Serum potassium levels meq/dl	Duration of hospital stay days	Duration of mechanical ventilation days		
1	M	58	Prophenophos	2.6	10	5	138	Death
2	M	50	Monochrotophos	3.1	6	3	136	Discharged
3	M	55	Monochrotophos	2.8	4	4	139	Death
4	F	28	Parathion	3	14	10	135	Discharged
5	M	58	Chlorthiophos	4.1	6	3	138	Death
6	M	27	Methyl parathion	2.8	6	3	138	Discharged
7	M	24	Chlorpyriphos	4.2	5	1	137	Discharged
8	M	21	Parathion	4.5	5	0	137	Discharged
9	M	25	Parathion	3	5	0	135	Discharged
10	F	25	Monochrotophos	2.4	10	5	136	Death
11	M	23	Diazinon	4.8	5	0	134	Discharged
12	M	23	Monochrotophos	4.5	5	0	137	Discharged
13	M	45	Monochrotophos	3	7	4	140	Discharged
14	M	21	Malathion	2.4	5	2	139	Discharged
15	M	24	Chlorpyriphos	2.5	9	2	139	Discharged
16	F	24	Monochrotophos	4.2	10	4	135	Discharged
17	M	55	Monochrotophos	2.1	2	2	138	Death
18	F	19	Methyl parathion	3	5	0	136	Discharged
19	F	40	Monochrotophos	4.6	5	0	137	Discharged
20	M	35	Anilphos	4.9	5	0	134	Discharged
21	M	30	Monochrotophos	2.3	4	4	137	Death
22	M	32	Phosphomidon	5.2	5	0	138	Discharged
23	M	25	Chlorpyriphos	2.6	6	4	136	Death

24	M	31	Chlorpyriphos	5	7	0	139	Discharged
25	M	50	Chlorpyriphos	2.8	13	4	137	Discharged
26	M	30	Monochrotophos	4.8	7	7	138	Death
27	M	60	Monochrotophos	2.4	2	2	140	Death
28	M	26	Temephos	5.2	9	3	135	Discharged
29	M	28	Fenthion	3	7	4	139	Death
30	M	45	Monochrotophos	5	5	1	137	Discharged
31	M	45	Chlorpyriphos	5.3	9	2	136	Discharged
32	M	50	Malathion	2	5	0	138	Discharged
33	F	35	Diazinon	4.9	5	0	134	Discharged
34	F	35	Monochrotophos	4.8	5	0	135	Discharged
35	F	25	Fenthion	4.4	4	0	133	Discharged
36	M	25	Methyl parathion	4.5	4	0	137	Discharged
37	M	55	Chlorthiophos	3.1	6	0	133	Discharged
38	M	42	Chlorpyriphos	2.7	3	3	136	Death
39	M	51	Chlorpyriphos	4.7	4	0	139	Discharged
40	M	40	Monochrotophos	2.3	6	6	131	Death
41	M	28	Chlorpyriphos	2.8	5	0	138	Discharged
42	M	42	Temephos	4.8	8	3	137	Discharged
43	F	45	Acephate	5	3	3	136	Death
44	M	25	Dimethoate	5.2	18	6	140	Discharged
45	M	56	Chlorpyriphos	3.1	6	0	133	Discharged
46	F	25	Triazophos	3	5	0	135	Discharged
47	M	15	Triazophos	4.5	6	0	138	Discharged
48	M	35	Diazinon	4.8	4	0	136	Discharged
49	F	22	Monochrotophos	4.7	5	0	135	Discharged
50	M	75	Chlorpyriphos	4.9	4	4	138	Death

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

EC RegNo.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.I.Mariraj,
PG in MD General medicine
Madras Medical College, Chennai-3.

Dear Dr. I.Mariraj

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Hypokalemia in Organophosphorous compound poisoning" No.30072013.

The following members of Ethics Committee were present in the meeting held on 02.07.2013 conducted at Madras Medical College, Chennai -3.

1. . Dr.G.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. Kalai Selvi -- Member
   Prof of Pharmacology, MMC, Ch-3
6. Prof. Siva Subramanian, -- Member
   Director, Instt. of Internal Medicine, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandhini 12/7/13
Member Secretary, Ethics Committee

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First 100 words of your submission

INTRODUCTION Organophosphorus compounds(OPCs) are common pesticides used in agriculture in India. Inappropriate handling, easier availability, and lack of adequate knowledge contribute to increased incidence of poisoning with these compounds in India which are also responsible for associated worse outcomes. Poisoning holds fourth position in leading causes of death in India. According to statistics given by WHO, approximately a million cases of accidental and about 2 million cases of suicidal attempts using insecticides occur worldwide annually. Many factors influence outcome in OPC poisoning like severity of poisoning, development of respiratory failure, availability of mechanical...